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NEWS	2	JUL 28	CA/CAplus patent coverage enhanced
NEWS	3	JUL 28	EPFULL enhanced with additional legal status information from the epoline Register
NEWS	4	JUL 28	IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
NEWS	5	JUL 28	STN Viewer performance improved
NEWS	6	AUG 01	INPADOCDB and INPAFAMDB coverage enhanced
NEWS	7	AUG 13	CA/CAplus enhanced with printed Chemical Abstracts page images from 1967-1998
NEWS	8	AUG 15	CAOLD to be discontinued on December 31, 2008
NEWS	9	AUG 15	CAplus currency for Korean patents enhanced
NEWS	10	AUG 27	CAS definition of basic patents expanded to ensure comprehensive access to substance and sequence information
NEWS	11	SEP 18	Support for STN Express, Versions 6.01 and earlier, to be discontinued
NEWS	12	SEP 25	CA/CAplus current-awareness alert options enhanced to accommodate supplemental CAS indexing of exemplified prophetic substances
NEWS	13	SEP 26	WPIDS, WPINDEX, and WPIX coverage of Chinese and and Korean patents enhanced
NEWS	14	SEP 29	IFICLS enhanced with new super search field
NEWS	15	SEP 29	EMBASE and EMBAL enhanced with new search and display fields
NEWS	16	SEP 30	CAS patent coverage enhanced to include exemplified prophetic substances identified in new Japanese-language patents
NEWS	17	OCT 07	EPFULL enhanced with full implementation of EPC2000
NEWS	18	OCT 07	Multiple databases enhanced for more flexible patent number searching
NEWS	19	OCT 22	Current-awareness alert (SDI) setup and editing enhanced
NEWS	20	OCT 22	WPIDS, WPINDEX, and WPIX enhanced with Canadian PCT Applications
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AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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FULL ESTIMATED COST 0.21 0.21

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DICTIONARY FILE UPDATES: 4 NOV 2008 HIGHEST RN 1070859-34-5

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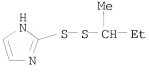
=> s 141400-58-1
L1 0 141400-58-1

=> s 141400-58-0
L2 1 141400-58-0
(141400-58-0/RN)

=> d L2 rn str cn

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2008 ACS on STN
RN 141400-58-0 REGISTRY



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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

CN   1H-Imidazole, 2-[(1-methylpropyl)dithio]-  (CA INDEX NAME)
OTHER NAMES:
CN   PX 12


=> file caplus medline embase biosis
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   8.07       8.28

FILE 'CAPLUS' ENTERED AT 13:40:12 ON 05 NOV 2008
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=> s 141400-58-0
L3          24 141400-58-0

=> dup rem L3
PROCESSING COMPLETED FOR L3
L4           24 DUP REM L3 (0 DUPLICATES REMOVED)

=> s polymer
L5     1855632 POLYMER

=> s L4 and L5
L6           1 L4 AND L5

=> s gelatin or cellulose
L7      640051 GELATIN OR CELLULOSE

=> s L3 and L7
L8           1 L3 AND L7

=> s L6 NOT L8
L9           0 L6 NOT L8

=> d L6 ibib abs

L6   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2004:490449  CAPLUS
DOCUMENT NUMBER:          141:42925
TITLE:                    Asymmetric disulfides for restoring normal cellular
                          functions
INVENTOR(S):              Kirkpatrick, Lynn; Powis, Garth
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S.
                          Ser. No. 366,751.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
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PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040116496	A1	20040617	US 2003-617949	20030710
WO 9824472	A1	19980611	WO 1997-US22292	19971205
W: AL, AT, BA, BB, BG, BR, CA, CH, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6552060	B1	20030422	US 1998-132421	19980811
US 20020055131	A1	20020509	US 2001-875578	20010606
US 6689775	B2	20040210		
US 20030176512	A1	20030918	US 2003-366751	20030214
CA 2573060	A1	20050127	CA 2004-2573060	20040712
WO 2005007108	A2	20050127	WO 2004-US22280	20040712
WO 2005007108	A3	20050825		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
US 1996-31995P	P	19961206
US 1997-55201P	P	19970811
WO 1997-US22292	W	19971205
US 1998-132421	A1	19980811
US 1999-319292	B1	19990603
US 2001-875578	A2	20010606
US 2003-366751	A2	20030214
US 2003-617949	A	20030710
WO 2004-US22280	W	20040712

AB The present invention is directed to a composition or formulation which includes an asym. disulfide which alone or in combination inhibits or interferes with cellular redox function, as well as a method of using same to restore normal cellular function. More specifically, the composition of the present invention is delivered to the patient over a period of time and interacts with, interfere with, or inhibits abnormal cellular proliferation and restores or prevents inhibition of cellular apoptosis. The asym. disulfide, preferably 1-methylpropyl-2-imidazolyldisulfide, is i.v. or orally administered to inhibit the abnormal cell growth, such as FAP polyps and angiogenesis.

=> d L4 1-24 ibib abs

L4 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2008:1185121 CAPLUS
DOCUMENT NUMBER:	149:420523
TITLE:	Method of extracting chromatin fractions from intact cells
INVENTOR(S):	Rodriguez-Collazo, Pedro; Leuba, Sanford Harrison; Zlafanova, Jordanka
PATENT ASSIGNEE(S):	USA

SOURCE: U.S. Pat. Appl. Publ., 29pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20080241845	A1	20081002	US 2008-61234	20080402
PRIORITY APPLN. INFO.:			US 2007-909491P P	20070402

AB Methods are provided for isolation of chromatin fractions of nucleoproteins containing histone H1, H2A, H2B, H3 and H4 proteins and/or histone H1, H2A, H2B, H3 and/or H4 proteins, from intact cells. The methods preserve original patterns of covalent modifications of the histone proteins.

L4 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:64825 CAPLUS
DOCUMENT NUMBER: 148:322142
TITLE: 2-[(1-Methylpropyl)dithio]-1H-imidazole inhibits tubulin polymerization through cysteine oxidation
AUTHOR(S): Huber, Kelly; Patel, Poulam; Zhang, Lei; Evans, Helen; Westwell, Andrew D.; Fischer, Peter M.; Chan, Stephen; Martin, Stewart
CORPORATE SOURCE: School of Molecular Medical Sciences, Division of Clinical Oncology, Nottingham University Hospitals, School of Pharmacy, University of Nottingham, Nottingham, UK
SOURCE: Molecular Cancer Therapeutics (2008), 7(1), 143-151
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 2-[(1-Methylpropyl)dithio]-1H-imidazole (IV-2) is a known inhibitor of the thioredoxin system. It causes the oxidation of cysteine residues from both thioredoxin reductase and thioredoxin, with only the latter leading to irreversible inhibition of protein function. Although IV-2 is considered to be the first specific inhibitor of thioredoxin to undergo evaluation in cancer patients (under the name PX-12), it is unclear whether the oxidative ability of IV-2 is limited to proteins of the thioredoxin family. The current study investigated the specificity of IV-2 by examining its interaction with tubulin, a protein in which cysteine oxidation causes loss of polymerization competence. The cellular effects of IV-2 were examined in MCF-7 breast cancer and endothelial cells (human umbilical vein endothelial cells). Immunocytochem. revealed a loss of microtubule structure with Western blot anal. confirming that treated cells contained a higher proportion of unpolymd. tubulin. Cell-free tubulin polymerization assays showed a dose-dependent inhibition of tubulin polymerization and depolymn. of preformed microtubules, confirming a direct interaction between IV-2 and tubulin. Further investigation of the tubulin interaction, through anal. of sulfhydryl reactivity and disulfide bond formation, suggested that IV-2 acts through the oxidation of cysteines in tubulin. Biochem. assays indicated that the oxidative properties of IV-2 are not limited to thioredoxin and tubulin, as cysteine-dependent proteases were also inhibited. Breast cancer cells with thioredoxin silenced by short interfering RNA remained sensitive to IV-2, albeit at higher antiproliferative GI50 values than in cells with normal thioredoxin function. These findings show that modulation of targets other than thioredoxin contribute to the effects of IV-2 on proliferating cells. [Mol

Cancer Ther 2008;7(1):143-51].
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:369854 CAPLUS
DOCUMENT NUMBER: 147:314431
TITLE: A Phase I Pharmacokinetic and Pharmacodynamic Study of PX-12, a Novel Inhibitor of Thioredoxin-1, in Patients with Advanced Solid Tumors
AUTHOR(S): Ramanathan, Ramesh K.; Kirkpatrick, D. Lynn; Belani, Chandra P.; Friedland, David; Green, Sylvan B.; Chow, H-H. Sherry; Cordova, Catherine A.; Stratton, Steven P.; Sharlow, Elizabeth R.; Baker, Amanda; Dragovich, Tomislav
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
SOURCE: Clinical Cancer Research (2007), 13(7), 2109-2114
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PURPOSE: Thioredoxin-1 (Trx-1) is a cellular redox protein that promotes tumor growth, inhibits apoptosis, and up-regulates hypoxia-inducible factor-1α and vascular endothelial growth factor. Objectives of this study were to determine safety, tolerability, pharmacodynamics, and pharmacokinetics of PX-12, a small-mol. inhibitor of Trx-1. Exptl. DESIGN: Thirty-eight patients with advanced solid tumors received PX-12 at doses of 9 to 300 mg/m2, as a 1- or 3-h i.v. infusion on days 1 to 5, repeated every 3 wk. RESULTS: At the 300 mg/m2 dose level, one patient experienced a reversible episode of pneumonitis during the first cycle, and a second patient developed pneumonitis after the second cycle. Doses up to 226 mg/m2 were well tolerated, and grade 3/4 events were uncommon (<3% of patients). The limiting factor on this dosing schedule was pungent odor caused by expired drug metabolite, 2-butanethiol. The best response was stable disease in seven patients (126-332 days). Whereas PX-12 was not detectable following the infusion, the Cmax of its inactive metabolite, 2-mercaptoimidazole, increased linearly with dose. PX-12 treatment lowered plasma Trx-1 concns. in a dose-dependent manner. CONCLUSIONS: PX-12, the first Trx-1 inhibitor to enter clin. trials, was tolerated up to a dose of 226 mg/m2 by a 3-h infusion. Based on pharmacodynamic and pharmacokinetic data, a trial of prolonged infusion schedule of PX-12 has been initiated.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:1286049 CAPLUS
DOCUMENT NUMBER: 146:20274
TITLE: Determination of HIF-1α inhibitor treatment response
INVENTOR(S): Kirkpatrick, Lynn; Pestano, Linda Anne
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 28pp., Cont.-in-part of U.S. Ser. No. 929,156.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060275836	A1	20061207	US 2006-379034	20060417
US 20050026872	A1	20050203	US 2004-929156	20040830
US 7399785	B2	20080715		
PRIORITY APPLN. INFO.:			US 2004-929156	A2 20040830
			US 2005-671765P	P 20050415
			US 2002-288888	A1 20021106

AB This invention relates to methods of measuring HIF expression and activity, as well as measuring inhibition of HIF following administration of an HIF inhibitor useful in treating HIF related diseases. The invention further relates to methods of identifying individuals who will respond to HIF inhibitors. The invention also relates to methods of monitoring a patient response to a given dosage of an HIF inhibitor. The invention also includes assays and kits for performing the methods described herein.

L4 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2007:71951 CAPLUS
DOCUMENT NUMBER:	146:219923
TITLE:	Drug evaluation: the thioredoxin inhibitor PX-12 in the treatment of cancer
AUTHOR(S):	Galmarini, Carlos M.
CORPORATE SOURCE:	EA3737 Pathologie des Cellules Lymphoides, UFR de Medecin Lyon-Sud, Centre Hospitalier Lyon-Sud, Universite Claude Bernard Lyon 1, Pierre-Benite, 69495, Fr.
SOURCE:	Current Opinion in Investigational Drugs (Thomson Scientific) (2006), 7(12), 1108-1115 CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER:	Thomson Scientific
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review. Biomira Inc, following its acquisition of ProIX Pharmaceutical Corp, is developing PX-12, an inhibitor of thioredoxin, for the potential treatment of cancer. PX-12 has completed phase I clin. trials.

REFERENCE COUNT:	57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2006:110292 CAPLUS
DOCUMENT NUMBER:	145:95883
TITLE:	The antitumor thioredoxin-1 inhibitor PX-12 (1-methylpropyl 2-imidazolyl disulfide) decreases thioredoxin-1 and VEGF levels in cancer patient plasma
AUTHOR(S):	Baker, Amanda F.; Dragovich, Tomislav; Tate, Wendy R.; Ramanathan, Ramesh K.; Roe, Denise; Hsu, Chiu-Hsieh; Kirkpatrick, D. Lynn; Powis, Garth
CORPORATE SOURCE:	Arizona Cancer Center, University of Arizona, Tucson, AZ, USA
SOURCE:	Journal of Laboratory and Clinical Medicine (2006), 147(2), 83-90 CODEN: JLCMAK; ISSN: 0022-2143
PUBLISHER:	Elsevier
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Thioredoxin-1 (Trx-1) is a small redox protein that is overexpressed in many human tumors, where it is associated with aggressive tumor growth and decreased patient survival. Trx-1 is secreted by tumor cells and is present at increased levels in the plasma of cancer patients. PX-12 is an irreversible inhibitor of Trx-1 currently in clin. development as an antitumor agent. We have used SELDI-TOF mass spectroscopy to measure

plasma Trx-1 from patients treated with PX-12 during a phase I study. Mean plasma Trx-1 levels at pretreatment were significantly elevated in the cancer patients at 182.0 ng/mL compared with 27.1 ng/mL in plasma from healthy volunteers. PX-12 treatment significantly lowered plasma Trx-1 in cancer patients having the highest plasma Trx-1 pretreatment levels. High-plasma vascular endothelial growth factor (VEGF) levels have been correlated to decreased patient survival. PX-12 treatment also significantly lowered plasma VEGF levels in cancer patients with high pretreatment VEGF levels. SELDI-TOF mass spectrometry identified seven addnl. plasma proteins whose levels decreased after PX-12 administration, one of which was identified as a truncated form of transthyretin. The results of this study suggest that the lowering of elevated levels of plasma Trx-1 in cancer patients may provide a surrogate for the inhibition of tumor Trx-1 by PX-12. Furthermore, PX-12 decreases plasma VEGF levels that may contribute to the antitumor activity of PX-12.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:271357 CAPLUS

DOCUMENT NUMBER: 142:385270

TITLE: The Thioredoxin-1 Inhibitor 1-Methylpropyl 2-Imidazolyl Disulfide (PX-12) Decreases Vascular Permeability in Tumor Xenografts Monitored by Dynamic Contrast Enhanced Magnetic Resonance Imaging

AUTHOR(S): Jordan, Benedicte F.; Runquist, Matthew; Raghunand, Natarajan; Gillies, Robert J.; Tate, Wendy R.; Powis, Garth; Baker, Amanda F.

CORPORATE SOURCE: Departments of Biochemistry, University of Arizona, Tucson, AZ, USA

SOURCE: Clinical Cancer Research (2005), 11(2, Pt. 1), 529-536 CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purpose: The purpose of this study was to use dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) to measure changes in tumor xenograft permeability produced by the antitumor thioredoxin-1 (Trx-1) inhibitor 1-methylpropyl 2-imidazolyl disulfide (PX-12) and to assess the relationship to Trx-1 and vascular endothelial growth factor (VEGF) levels. Exptl. Design: DCE-MRI was used to monitor the dynamics of gadolinium-diethylenetriaminepentaacetic acid coupled bovine serum albumin as a macromol. contrast reagent to measure hemodynamic changes in HT-29 human colon xenografts in immunodeficient mice treated with PX-12. Blood vessel permeability was estimated from the slope of the enhancement curves, and tumor vascular volume fraction from the ordinate. Tumor Trx-1 and VEGF was also measured. Results: PX-12 caused a rapid 63% decrease in the average tumor blood vessel permeability within 2 h of administration. The decrease lasted 24 h and had returned to pretreatment values by 48 h. The changes in vascular permeability were not accompanied by alterations in average tumor vascular volume fraction. There was a decrease in tumor and tumor-derived VEGF in plasma at 24 h after treatment with PX-12, but not at earlier time points. However, tumor redox active Trx-1 showed a rapid decline within 2 h following PX-12 administration that was maintained for 24 h. Conclusion: The rapid decrease in tumor vascular permeability caused by PX-12 administration coincided with a decrease in tumor redox active Trx-1 and preceded a decrease in VEGF. DCE-MRI responses to PX-12 in patients of Trx-1 inhibition at early time points and decreased VEGF at later times, may be useful to follow tumor response and even therapeutic benefit.

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:490449 CAPLUS
DOCUMENT NUMBER: 141:42925
TITLE: Asymmetric disulfides for restoring normal cellular functions
INVENTOR(S): Kirkpatrick, Lynn; Powis, Garth
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 366,751.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040116496	A1	20040617	US 2003-617949	20030710
WO 9824472	A1	19980611	WO 1997-US22292	19971205
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RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6552060	B1	20030422	US 1998-132421	19980811
US 20020055131	A1	20020509	US 2001-875578	20010606
US 6689775	B2	20040210		
US 20030176512	A1	20030918	US 2003-366751	20030214
CA 2573060	A1	20050127	CA 2004-2573060	20040712
WO 2005007108	A2	20050127	WO 2004-US22280	20040712
WO 2005007108	A3	20050825		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
US 1996-31995P	P	19961206
US 1997-55201P	P	19970811
WO 1997-US22292	W	19971205
US 1998-132421	A1	19980811
US 1999-319292	B1	19990603
US 2001-875578	A2	20010606
US 2003-366751	A2	20030214
US 2003-617949	A	20030710
WO 2004-US22280	W	20040712

AB The present invention is directed to a composition or formulation which includes an asym. disulfide which alone or in combination inhibits or interferes with cellular redox function, as well as a method of using same to restore normal cellular function. More specifically, the composition of the present invention is delivered to the patient over a period of time and interacts with, interfere with, or inhibits abnormal cellular proliferation and restores or prevents inhibition of cellular apoptosis. The asym. disulfide, preferably 1-methylpropyl-2-imidazolyldisulfide, is

i.v. or orally administered to inhibit the abnormal cell growth, such as FAP polyps and angiogenesis.

L4 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:757707 CAPLUS
DOCUMENT NUMBER: 141:343051
TITLE: Thioredoxin Reductase as a Potential Molecular Target for Anticancer Agents That Induce Oxidative Stress
AUTHOR(S): Smart, DeeDee K.; Ortiz, Karen L.; Mattson, David; Bradbury, C. Matthew; Bisht, Kheem S.; Sieck, Leah K.; Brechbiel, Martin W.; Gius, David
CORPORATE SOURCE: Molecular Radiation Oncology Section and Radioimmune and Inorganic Chemistry Section, Radiation Oncology Branch, Radiation Oncology Sciences Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Cancer Research (2004), 64(18), 6716-6724
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Redox-sensitive signaling factors regulate multiple cellular processes, including proliferation, cell cycle, and prosurvival signaling cascades, suggesting their potential as mol. targets for anticancer agents. It is logical to set constraints that a mol. target should meet at least one of the following criteria: (1) inhibition of prosurvival signaling pathways; (2) inhibition of cell cycle progression; or (3) enhancement of the cytotoxic effects of anticancer agents. Therefore, the authors hypothesized that thioredoxin reductase 1 (TR), a component of several redox-regulated pathways, might represent a potential mol. target candidate in response to agents that induce oxidative stress. To address this issue, permanent cell lines overexpressing either the wild-type (pCXN2-myc-TR-wt) or a Cys-Ser mutant (pCXN2-myc-mTR) TR gene were used, as were parental HeLa cells treated with 1-methyl-1-propyl-2-imidazolyl disulfide (IV-2), a pharmacol. inhibitor of TR. Cells were exposed to the oxidative stressors, H2O2 and ionizing radiation (IR), and analyzed for changes in signal transduction, cell cycle, and cytotoxicity. Anal. of HeLa cells overexpressing the pCXN2-myc-TR-wt gene showed increased basal activity of nuclear factor κB (NFκB) and activator protein (AP-1), whereas HeLa cells expressing a pCXN2-myc-mTR gene and HeLa cells treated with IV-2 were unable to induce NFκB or AP-1 activity following H2O2 or IR exposure. Fluorescence-activated cell sorting anal. showed a marked accumulation of pCXN2-myc-mTR cells in the late G1 phase, whereas pCXN2-myc-TR-wt cells showed a decreased G1 subpopulation. Chemical inhibition of TR with IV-2 also completely inhibited cellular proliferation at concns. between 10 and 25 μmol/L, resulting in a G1 phase cell cycle arrest consistent with the results from cells expressing the pCXN2-myc-mTR gene. Following exposure to H2O2 and IR, pCXN2-myc-mTR- and IV-2-treated cells were significantly more sensitive to oxidative stress-induced cytotoxicity as measured by clonogenic survival assays. Finally, IV-2-treated cells showed increased tumor cell death when treated with H2O2 and IR. These results identify TR as a potential target to enhance the cytotoxic effects of agents that induce oxidative stress, including IR.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:315621 CAPLUS
DOCUMENT NUMBER: 138:314629
TITLE: Asymmetric disulfides and use in redox function-based

modulation of cellular function
INVENTOR(S): Kirkpatrick, D. Lynn
PATENT ASSIGNEE(S): Prolx Pharmaceuticals, Inc., USA
SOURCE: U.S., 28 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6552060	B1	20030422	US 1998-132421		19980811
US 2003017652	A1	20030918	US 2003-366751		20030214
US 20040116496	A1	20040617	US 2003-617949		20030710
PRIORITY APPLN. INFO.:			US 1997-55201P	P	19970811
			US 1996-31995P	P	19961206
			WO 1997-US22292	W	19971205
			US 1998-132421	A1	19980811
			US 1999-319292	B1	19990603
			US 2001-875578	A2	20010606
			US 2003-366751	A2	20030214

OTHER SOURCE(S): MARPAT 138:314629
AB The invention provides a composition or formulation which includes an asym. disulfide which alone or in combination inhibits or interferes with cellular redox function, as well as a method of use to restore normal cellular function. More specifically, the composition of the invention interacts with, interferes with, or inhibits abnormal cellular proliferation and restores or prevents inhibition of cellular apoptosis. Preparation of compds. using a combinatorial synthetic method, as well as evaluation of biol. activity, are included.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:238985 CAPLUS
DOCUMENT NUMBER: 139:143631
TITLE: The thioredoxin redox inhibitors 1-methylpropyl-2-imidazolyl disulfide and pleurotin inhibit hypoxia-induced factor 1α and vascular endothelial growth factor formation
AUTHOR(S): Welsh, Sarah J.; Williams, Ryan R.; Birmingham, Anne; Newman, David J.; Kirkpatrick, D. Lynn; Powis, Garth
CORPORATE SOURCE: Arizona Cancer Center, Tucson, AZ, 85724, USA
SOURCE: Molecular Cancer Therapeutics (2003), 2(3), 235-243
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hypoxia-inducible factor-1 (HIF-1) is a transcription factor that plays a critical role in tumor growth by increasing resistance to apoptosis and the production of angiogenic factors such as vascular endothelial growth factor (VEGF). HIF-1 is a heterodimer comprised of oxygen-regulated HIF-1α and constitutively expressed HIF-1β subunits. The redox protein thioredoxin-1 (Trx-1), which is found at high levels in many human cancers, increases both aerobic and hypoxia-induced HIF-1α protein in cells leading to increased expression of HIF-regulated genes. We have investigated whether two cancer drugs that inhibit Trx-1 signaling, PX-12 (1-methylpropyl 2-imidazolyl disulfide) and pleurotin, decrease HIF-1α protein levels and the expression of downstream target genes. Treatment of MCF-7 human breast cancer and HT-29 human colon carcinoma cells with PX-12 and pleurotin prevented the hypoxia (1% oxygen)-induced

increase in HIF-1α protein. HIF-1-trans-activating activity, VEGF formation, and inducible nitric oxide synthase were also decreased by treatment with PX-12 and pleurotin under hypoxic conditions. PX-12 and pleurotin also decreased HIF-1α protein levels and HIF-1 trans-activation in RCC4 renal cell carcinoma cells that constitutively overexpress HIF-1α protein because of loss of the pVHL gene, indicating that HIF-1α is inhibited independently of the pVHL pathway. HIF-1α and VEGF protein levels in MCF-7 tumor xenografts in vivo were decreased by PX-12 treatment of mice. The results suggest that inhibition of HIF-1α by Trx-1 inhibitors may contribute to the growth inhibitory and antitumor activity of these agents.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:508169 CAPLUS

DOCUMENT NUMBER: 138:243030

TITLE: Solubility, ionization, and partitioning behavior of unsymmetrical disulfide compounds: alkyl 2-imidazolyl disulfides

AUTHOR(S): Hashash, Ahmad; Kirkpatrick, D. Lynn; Lazo, John S.; Block, Lawrence H.

CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Mellon Hall of Sciences, Duquesne University, Pittsburgh, PA, 15282, USA

SOURCE: Journal of Pharmaceutical Sciences (2002), 91(7), 1686-1692
CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Alkyl 2-imidazolyl disulfide compds. are novel antitumor agents, one of which is currently being evaluated in Phase I clin. trials. These mols. contain an unsym. disulfide fragment, the lipophilic and electronic contributions of which are still not defined in the literature. Lipophilicity, ionization, and solubility of a number of alkyl 2-imidazolyl disulfides were studied. Based on the additivity of lipophilicity and ionization properties, the contribution of the unsym. disulfide fragment to lipophilicity and ionization was elucidated. The unsym. disulfide fragment contributed a Rekker's hydrophobic constant of 0.761 to the lipophilicity of these compds. and an approximated Hammett constant (σ) of 0.30 to their ionization. The applicability of the general solubility equation (GSE) proposed by Jain and Yalkowsky in predicting the aqueous solubility of these analogs was evaluated. The GSE correctly ranked the aqueous solubilities of these compds. and estimated their log molar solubilities with an average absolute error of 0.35.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:908622 CAPLUS

DOCUMENT NUMBER: 139:30687

TITLE: Enhancement of metabolic oxidative stress-induced cytotoxicity by the thioredoxin inhibitor 1-methylpropyl 2-imidazolyl disulfide is mediated through the ASK1-SEK1-JNK1 pathway

AUTHOR(S): Lee, Yong J.; Kim, Jin H.; Chen, Jun; Song, Jae J.

CORPORATE SOURCE: Department of Surgery, Pharmacology and Cancer Institute, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

SOURCE: Molecular Pharmacology (2002), 62(6), 1409-1417
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We observed previously that glucose deprivation induces cytotoxicity, increases the intracellular levels of hydroperoxide, and activates the stress-activated protein kinase (SEK) pathway. In this study, we hypothesized that 1-methylpropyl 2-imidazolyl disulfide (IV-2), a thioredoxin (TRX) inhibitor, augments glucose deprivation-induced cytotoxicity by promoting c-Jun N-terminal kinase (JNK) activation. Human prostatic carcinoma DU-145 cells were exposed to glucose-free medium containing various concns. of IV-2 (10-50 μM). Glucose deprivation alone or IV-2 alone induced minimal cytotoxicity within 7 h. However, the combination of glucose deprivation and IV-2 increased cell death in a dose-dependent manner. The cytotoxicity was suppressed by treatment with an antioxidant, N-acetyl-L-cysteine or overexpressing TRX. The combined glucose deprivation and IV-2 treatment also promoted glucose deprivation-induced JNK1 activation by disrupting the interaction between TRX and apoptosis signal-regulating kinase 1 (ASK1). Overexpression of the JNK1 dominant-neg. mutant inhibited the activation of the SEK pathway and protected cells from glucose deprivation and IV-2-induced cytotoxicity. Therefore, IV-2 enhances glucose deprivation-induced cytotoxicity by promoting glucose deprivation-induced activation of the ASK1-SEK1-JNK1 pathway.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:118612 CAPLUS
DOCUMENT NUMBER: 136:350088
TITLE: Normal-phase and stability-indicating reversed-phase high-performance liquid chromatographic methods for the determination of the novel antitumor agent: 1-methylpropyl-2-imidazolyldisulfide
AUTHOR(S): Hashash, Ahmad; Lynn Kirkpatrick, D.; Egorin, Merrill J.; Block, Lawrence H.; Lazo, John S.
CORPORATE SOURCE: Duquesne University, Graduate School of Pharmaceutical Sciences, Pittsburgh, PA, 15282, USA
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2002), 768(2), 239-246
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1-Methylpropyl-2-imidazolyl disulfide (MID) is a novel antitumor agent currently in Phase I clin. trials. The chromatog. behavior of MID and its potential impurity, degradation product, and metabolite 2-mercaptoimidazole (2MI) was studied under reversed-phase (RP) and normal-phase (NP) conditions. Both RP- and NP-HPLC separation methods were developed. RP-HPLC was validated as a stability-indicating assay for MID. NP-HPLC retained both MID and 2MI and pending further validation, could prove useful in the study of MID pharmacokinetics.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:618211 CAPLUS
DOCUMENT NUMBER: 135:175341
TITLE: DNA arrays for determining drug selectivity

INVENTOR(S): Kirkpatrick, D. Lynn; Powis, Garth; Miller, Raymond A.
PATENT ASSIGNEE(S): Prolx Pharmaceuticals, LP, USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001061052	A1	20010823	WO 2001-US5382	20010216

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-502246 A 20000217

AB Generally the present invention is directed to a method of screening drug candidates as well as to compns. identified thereby. Hybridization expts. utilize the immobilized sequences as "bait" which are used to analyze a mix of targets, which are the cDNAs derived be reverse transcription (RT) of cellular mRNA. Fluorescently-tagged nucleotides are included in the RT reactions, so that the RT-PCR generated cDNA will be fluorescently labeled. The binding of the labeled cDNA to the template DNA can be evaluated by confocal microscopy of the slide under laser illumination. Statistical and comparative anal. of the resulting data shows which genes are significantly expressed.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:743282 CAPLUS
DOCUMENT NUMBER: 136:144764
TITLE: Thioredoxin expression in primary T-cell acute lymphoblastic leukemia and its therapeutic implication
AUTHOR(S): Shao, Li-En; Diccianni, Mitchell B.; Tanaka, Tetsuya; Gribi, Ruby; Yu, Alice L.; Pullen, Jeanette D.; Camitta, Bruce M.; Yu, John
CORPORATE SOURCE: Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Cancer Research (2001), 61(19), 7333-7338
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Increased expression of intracellular thioredoxin has been implicated in the inhibition of apoptosis and in a decrease in the sensitivity of the malignancies to drug-induced apoptosis. In the present studies, we analyzed expression of thioredoxin in samples from 28 children with T-cell acute lymphoblastic leukemia and analyzed their sensitivity toward inhibition of thioredoxin expression. Thioredoxin was expressed in variable amts. Higher expression was associated with higher WBC counts. Exogenously added thioredoxin stimulated proliferation of clonogenic cells among the T-cell acute lymphoblastic leukemia samples expressing relatively lower levels of intracellular thioredoxin, whereas there was no effect on the clonogenic cells expressing high levels of thioredoxin. In addition, there was differential sensitivity of the leukemia clonogenic cells

toward 1-methylpropyl 2-imidazolyl disulfide, an inhibitor of thioredoxin expression, as compared with normal hematopoietic progenitors. This suggests the possibility of using this approach for treatment. Because overexpression of thioredoxin is associated with resistance to many anticancer drugs, the inhibition of thioredoxin expression may overcome this drug resistance and probably sensitize leukemia cells to other chemotherapeutic agents.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:614461 CAPLUS

DOCUMENT NUMBER: 133:290771

TITLE: Antitumor imidazolyl disulfide IV-2 causes irreversible G2/M cell cycle arrest without hyperphosphorylation of cyclin-dependent kinase Cdk1

AUTHOR(S): Vogt, Andreas; Tamura, Kenji; Watson, Shawndra; Lazo, John S.

CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 294(3), 1070-1075
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Aberrant function of redox-regulated proteins is a possible cause for cellular transformation and loss of cell cycle control. The small protein thioredoxin has oncogenic properties and controls cell cycle movement through G1, S, and G2/M phases. The redox-active, asym. 1-methylpropyl-2-imidazolyl disulfide (IV-2) has previously been shown to react with and inhibit thioredoxin activity in vitro, the proliferation of human tumor cells in culture, and the growth of tumors in mice. We now examined the effects of IV-2 on cell cycle progression. In synchronized tsFT210 mouse mammary carcinoma cells, IV-2 halted cells in mitosis. In asynchronously growing MCF-7 human breast cancer cells, IV-2 exclusively and irreversibly blocked cells in G2/M at concns. that correlated with its growth inhibitory activity. Neither the closely related, less redox active 2-hydroxy-1-methylpropyl-2-imidazolyl disulfide (AIV-2), which differs from IV-2 only by an addnl. hydroxyl group, nor the sym. diallyl disulfide caused a G2/M arrest under these conditions. Furthermore, MCF-7 cells treated with IV-2 showed increased Cdk1 kinase activity and a decrease in Cdk1 tyrosine phosphorylation, indicating that IV-2 did not directly inhibit Cdk1 or Cdc25 activities. IV-2 did, however, increase Bcl-2 phosphorylation. These data suggest that the thioredoxin inhibitor IV-2, despite its simple structure, is able to target redox-sensitive processes that are critical for cell cycle progression through mitosis. The results are also consistent with a role of thioredoxin regulating cell cycle progression through G2/M.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:228539 CAPLUS

DOCUMENT NUMBER: 133:26478

TITLE: Parallel syntheses of disulfide inhibitors of the thioredoxin redox system as potential antitumor agents

AUTHOR(S): Kirkpatrick, D. Lynn; Watson, Shawndra; Kunkel, Mark; Fletcher, Susan; Ulhaq, Saraj; Powis, Garth

CORPORATE SOURCE: Department of Chemistry, University of Regina, Regina, SK, Can.

SOURCE: Anti-Cancer Drug Design (1999), 14(5), 421-432
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have reported previously that unsym. disulfide inhibitors of the human thioredoxin/thioredoxin reductase redox system (hTrx/TR) possess antitumor activity. The authors have broadened the search for more potent inhibitors and evaluated a large range of mono- and bis-disulfide compds., prepared using parallel syntheses. Reaction of isothioisourea-HCl salts (R') or bis-salts (R) with aromatic or aryl thiols (R") in wells of 96-well plates produced > 450 derivs. with the structures R"SSR' and R"SSRSSR". The excellent yield and purity of the disulfides provided sufficient material for evaluations of enzyme inhibition and cytotoxicity. Selection criteria based on the IC50 values for hTrx/TR inhibition and for cytotoxicities of the disulfides identified agents for subsequent scale-up syntheses and in vivo evaluations of antitumor activity. These scale-up studies confirmed the original activities of agents synthesized in the plates and validated the parallel synthetic approach. Structure-activity information derived from the hTrx/TR IC50 data allow for a number of generalizations. The most potent inhibitors of the Trx system contained two heteroatoms ortho to the disulfide moiety in an aromatic functionality. The thioalkylating moieties had greatest activity with one branch point alpha to the disulfide. In the absence of branching, more potent inhibition was observed with the electron withdrawing functionalities. Bis-disulfides showed patterns of activity which depended on chain length, with optimum activity observed when the disulfide units were separated by 3.9 Å, a similar distance to that separating the thioredoxin active site cysteine residues. From the agents selected for scale-up syntheses, three disulfide compds. were studied for their antitumor activity in vivo against human tumor xenografts in scid mice. From the agents selected for scale-up syntheses, three disulfide compds. were studied for their antitumor activity in vivo against human tumor xenografts in scid mice. One of the analogs discovered through the combinatorial syntheses/screening for Trx inhibition, 1-phenylethyl 2-imidazolyl disulfide, N1 (ProlX agent PX-C5), has demonstrated excellent in vivo activity against the MCF-7 human breast cancer and the HL-60 human leukemia, thus validating this approach for novel drug discovery.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:229894 CAPLUS
DOCUMENT NUMBER: 129:234
ORIGINAL REFERENCE NO.: 129:55a,58a
TITLE: Mechanisms of inhibition of the thioredoxin growth factor system by antitumor 2-imidazolyl disulfides
AUTHOR(S): Kirkpatrick, D. Lynn; Kuperus, Miles; Dowdeswell, Marla; Potier, Noelle; Donald, Lynda J.; Kunkel, Mark; Berggren, Margareta; Angulo, Miguel; Powis, Garth
CORPORATE SOURCE: Department of Chemistry, University of Regina, Regina, SK, S4S 0A2, Can.
SOURCE: Biochemical Pharmacology (1998), 55(7), 987-994
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The interactions of a series of 2-imidazolyl disulfide antitumor compds. with the thioredoxin reductase (TR)-thioredoxin (hTrx) redox system have been studied. Bu 2-imidazolyl disulfide (I) and Et 2-imidazolyl disulfide (II) were substrates for reduction by TR with Km values of 43 and 48 μM. 1-Methylpropyl 2-imidazolyl disulfide (III) and benzyl 2-imidazolyl

disulfide (IV) were competitive inhibitors of the reduction of hTrx by TR with Ki values of 31 μM. None of the disulfides were substrates for reduction by human glutathione reductase. The disulfides caused reversible thioalkylation of hTrx at the redox catalytic site as shown by the fact that there was no thioalkylation of a mutant hTrx where both the catalytic site Cys32 and Cys35 residues were replaced by Ser. In addition, the disulfides caused a slower irreversible inactivation of hTrx as a substrate for reduction by TR, with half-lives for I of 30 min, for III of 4 h, and for tert-Bu 2-imidazolyl disulfide of 24 h. This irreversible inactivation of hTrx occurred at concns. of the disulfides an order of magnitude below those that inhibited TR, and involved the Cys73 of hTrx, which is outside the conserved redox catalytic site, as shown by the resistance to inactivation of a mutant hTrx where Cys73 was replaced by Ser. Electrophoretic and mass spectral analyses of the products of the reaction between the disulfides and hTrx show that modification of 1-3 Cys residues of the protein occurred in a concentration-dependent fashion. The disulfides inhibited the hTrx-dependent proliferation of MCF-7 breast cancer cells with IC50 values of I and III of 0.2 and 1.2 μM, resp. The results show that although the catalytic sites of TR and hTrx are reversibly inhibited by the 2-imidazolyl disulfides, it is the irreversible thioalkylation of Cys73 of hTrx by the disulfides that most probably accounts for the inhibition of thioredoxin-dependent cell grown by the disulfides.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1998:27367 CAPLUS
DOCUMENT NUMBER: 128:162607
ORIGINAL REFERENCE NO.: 128:31862h,31863a
TITLE: Cell line-directed screening assay for inhibitors of thioredoxin reductase signaling as potential anti-cancer drugs
AUTHOR(S): Kunkel, Mark W.; Kirkpatrick, D. Lynn; Johnson, Jill I.; Powis, Garth
CORPORATE SOURCE: Arizona Cancer Center, University of Arizona Health Sciences Center, Tucson, AZ, 85724-5024, USA
SOURCE: Anti-Cancer Drug Design (1997), 12(8), 659-670
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have used a cell line-directed screening approach (CDSA) to identify novel inhibitors of the thioredoxin reductase signaling pathway which contributes to the transformed phenotype of some human tumors. Two 2-imidazolyl disulfide compds., previously identified as inhibitors of thioredoxin reductase, were screened for growth inhibitory activity in the National Cancer Institute (NCI) human cancer cell line panel. The COMPARE pattern recognition algorithm was used to identify similar compds. from >60,000 compds. in the NCI investigational drug database. Of 47 nondiscreet compds. tested in a thioredoxin reductase/thioredoxin insulin reduction assay, 37 (77%) were inhibitors with IC50s ≤ 10 μg/mL and 15 of those (32%) had IC50s ≤ 1 μg/mL. These compds. were all as selective or more selective for thioredoxin reductase than for glutathione reductase, while three compds. were inhibitors of thioredoxin. In comparison to CDSA, the number of compds. with IC50s ≤ 1 μg/mL identified by screening of 52 compds. from the database whose growth inhibiting activity was unrelated to the activity of the disulfide compds. was only 2%. Screening of 221 randomly selected natural products gave only 3% of compds. with IC50s ≤ 1 μg/mL. Thus, the CDSA using data from the NCI cancer cell panel and known inhibitors of the selected target as seed compds. can greatly increase hit rates, compared with

random screening, for identifying novel inhibitors of a target, in this case thioredoxin signaling.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:145310 CAPLUS
DOCUMENT NUMBER: 128:239119
ORIGINAL REFERENCE NO.: 128:47169a,47172a
TITLE: Redox active disulfides: the thioredoxin system as a drug target
AUTHOR(S): Kirkpatrick, D. Lynn; Ehrmantraut, Greg; Stettner, Shawndra; Kunkel, Mark; Powis, Garth
CORPORATE SOURCE: Department of Chemistry, University of Regina, Regina, SK, S4S 0A2, Can.
SOURCE: Oncology Research (1997), 9(6/7), 351-356
CODEN: ONREE8; ISSN: 0965-0407
PUBLISHER: Cognizant Communication Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thioredoxin, and particularly extracellular thioredoxin, presents an attractive target for developing novel agents to treat cancer. Our studies have involved the examination of a series of alkyl 2-imidazolyl disulfides as inhibitors of the growth-stimulatory activity of the thioredoxin system. We originally determined the disulfides to be weak reversible inhibitors of thioredoxin reductase. Subsequently, we have shown that alkyl 2-imidazolyl disulfides interact directly with thioredoxin, thioalkylating critical cysteine residues or causing dimerization of the protein leading to its loss of biol. activity. One of the analogs that binds to thioredoxin, 1-methylpropyl 2-imidazolyl disulfide (IV-2), selectively inhibits the thioredoxin-dependent growth of tumor cells in culture and has antitumor activity against MCF-7 and HL-60 tumors in vivo. Our work involves the development of a parallel combinatorial synthetic method to produce a large number of disulfide analogs at one time. These analogs, which differ sterically, electronically, and phys., were produced in a 96-well plate. The biol. activity of these analogs was evaluated, also in the 96-well plate format. This rapid method of evaluating biol. activity is a means to identify agents with specificity for inhibition of the thioredoxin system, and may provide novel antitumor agents with activity against solid tumor cancers.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

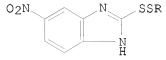
L4 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:523489 CAPLUS
DOCUMENT NUMBER: 123:47459
ORIGINAL REFERENCE NO.: 123:8275a,8278a
TITLE: The thioredoxin/thioredoxin reductase redox system and control of cell growth
AUTHOR(S): Powis, Garth; Oblong, John E.; Gasdaska, Pamela Y.; Berggren, Margareta; Hill, Simon R.; Kirkpatrick, D. Lynn
CORPORATE SOURCE: Arizona Cancer Center, Tucson, AZ, 85724, USA
SOURCE: Oncology Research (1994), 6(10-11), 539-44
CODEN: ONREE8; ISSN: 0965-0407
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thioredoxin is a redox protein that is important for a variety of intracellular functions, possibly including regulation of transcription factor activity. We have shown that human thioredoxin has the same predicted amino acid sequence as adult T-cell-derived leukemic cell growth

factor. Recombinant human thioredoxin stimulates the proliferation of Swiss murine 3T3 fibroblasts with an EC50 of 100 nM and the proliferation of a number of human cancer cells. Site-directed mutagenesis of the active-site cysteines of thioredoxin has shown that redox activity is necessary for the stimulation of cell proliferation. Added 125I-thioredoxin is taken up by cells in culture and could have intracellular action. A series of alkyl 2-imidazolyl disulfides have been shown to be competitive inhibitors of human thioredoxin reductase with Ki values of 3.3 to 8.6 μM. The compds. inhibited Swiss 3T3 serum-dependent proliferation with IC50 values of 2.0 to 4.0 μM, and one compound inhibited Swiss 3T3 thioredoxin-dependent proliferation with an IC50 value of 60 nM.

L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:221529 CAPLUS
DOCUMENT NUMBER: 122:285278
ORIGINAL REFERENCE NO.: 122:51867a,51870a
TITLE: Reversible inhibition of human thioredoxin reductase activity by cytotoxic alkyl 2-imidazolyl disulfide analogs
AUTHOR(S): Oblong, John E.; Chantler, Edmundo L.; Gallegos, Alfred; Kirkpatrick, D. Lynn; Chen, Tao; Marshall, Nicole; Powis, Garth
CORPORATE SOURCE: Arizona Cancer Center, Tucson, AZ, 85715, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1994), 34(5), 434-8
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of Bu 2-imidazolyl disulfide (III-2), 1-methylpropyl 2-imidazolyl disulfide (IV-2), and n-decyl 2-imidazolyl disulfide (VII-2) on purified human placental thioredoxin reductase activity were examined The analogs were competitive inhibitors with DTNB for reduction by thioredoxin reductase, with Ki values for III-2, IV-2, and VII-2 being 3.3, 13.0, and 8.6 μM, resp. The inhibition was noncompetitive with NADPH. None of the analogs was a suicide substrate inhibitor of the flavoenzyme. III-2 and VII-2 were metabolized by thioredoxin reductase at about half the rate of DTNB, whereas IV-2 was not detectably metabolized. The 2nd order rate consts. for the reactions of III-2 and IV-2 with GSH were 931 and 91 M-1 s-1, resp. The lower reactivity of IV-2 with GSH and the lack of the analog's metabolism by thioredoxin reductase may be due to the more sterically hindered structure of this analog. The 50% inhibitory concns. (IC50 values) for the inhibition of serum-dependent cellular proliferation of Swiss 3T3 murine fibroblasts by III-2, IV-2, and VII-2 were 2.0, 3.5, and 4.0 μM, resp. IV-2 was considerably more potent as an inhibitor of the thioredoxin-dependent cellular proliferation of Swiss 3T3 fibroblasts, showing an IC50 value of 60 nM. Thus, inhibition of cellular proliferation by alkyl 2-imidazolyl disulfide analogs may involve interaction with thioredoxin, thioredoxin reductase, or an alternative target that is redox regulated by thioredoxin.

L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1992:255539 CAPLUS
DOCUMENT NUMBER: 116:255539
ORIGINAL REFERENCE NO.: 116:43330h,43331a
TITLE: Synthesis and evaluation of imidazolyl disulfides for selective cytotoxicity to hypoxic EMT6 tumor cells in vitro
AUTHOR(S): Kirkpatrick, D. Lynn; Jimale, M. L.; King, K. M.; Chen, T.
CORPORATE SOURCE: Dep. Chem., Univ. regina, Regina, SK, S4S 0A2, Can.
SOURCE: European Journal of Medicinal Chemistry (1992), 27(1),

33-7
CODEN: EJMCA5; ISSN: 0223-5234
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

II

AB Two series of disulfides, benzimidazolyl disulfides I (R = Et, Pr, CHMe2, Bu, CHMeEt, CH2CHMe2) and imidazolyl disulfdes II, were synthesized and evaluated in vitro for selective hypoxic tumor cell cytotoxicity using EMT6 cells. Thus, 1-methyl-1-propanethiol condensed with thiourea to give 1-methyl-1-propanethioisothiourea which reacted with 2-mercaptoimidazole to give II (R = CHEtMe) in 79% yield. While the series of alkyl 5-nitrobenzimidazolyl disulfides displayed no selectivity, II (R = Et, Bu), showed preferential toxicity to EMT6 cells treated under hypoxic conditions.

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